

utilized in this study before any conclusions about clinical applicability in humans can be drawn.

The analogous clinical scenario in humans to the benchtop one depicted here in rats would be for a clinician to inject erythropoietin into the urethra immediately after a known (likely iatrogenic?) urethral injury so to prevent a possible urethral stricture. When is a urethra knowingly injured in a manner in which this scenario could be possible or even advisable? Almost never.

What researchers and clinicians alike are really looking for is a substance that can be injected into the urethra after urethrotomy for urethral stricture disease that will hasten scar reformation, keeping the urethral lumen open (>14F) and prevent the need for a urethroplasty.

There are a few candidates that have been investigated whose reported recurrence preventing mechanism is to modify (or prevent) collagen deposition after urethrotomy including, but not limited to, mitomycin,<sup>1</sup> triamcinolone,<sup>2</sup> and collagenase.<sup>3</sup> More recently, injectables that aim prevent recurrence by hastening endothelial and urethral regeneration, including Fat-derived Stem Cells,<sup>4</sup> platelet rich plasma<sup>5</sup> and even liquid buccal mucosa grafts<sup>6</sup> have also been described.

What do all of these injectables have in common? All of them are reported to provide clinical benefit. Why, then, are none of them being utilized routinely? – why are we still doing urethroplasties at all if they work so well? Most obvious is the need to follow these patients longer – and without well-designed RCTs, we'll never know to what degree the success can be attributed to the stricture characteristics, the urethrotomy or the injectable itself. Or perhaps these injectables just delay the recurrence (hence the initial enthusiasm) but don't prevent them (hence the lack of follow-up data or widespread adoption)?

However, more fundamentally, we likely don't have a winner yet because we don't understand how any of them work – and without an understanding of urethral stricture pathophysiology – how they form (nearly 60% of strictures are still labeled idiopathic!!), why they recur, and how they are related to other local and systemic disease processes<sup>7</sup> – we never will.

Add erythropoietin to the more recent amementarium of injectables that are hypothesized to help with local regeneration of tissue after urethrotomy for stricture disease. Though I believe regenerative injectables will be the key to eliminating the need for (most) urethroplasties, a specific modifiable target for the injectable within the stricture will need to be found first.

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## AUTHOR REPLY



The most important problem of urethral wound healing is an increase in abnormal fibrosis because of imbalances in the healing processes. Healing of traumatic or idiopathic wounds in the urethra is known to be complicated and a longer process than dermal healing with sequential yet overlapping phases of hemostasis, inflammation, proliferation, and remodeling.<sup>1</sup>

The history of wound healing is old as the history of humankind. The oldest known medical record is a clay tablet that was written around 2200 BC.<sup>2</sup> To ensure that a wound healed properly and quickly, a wide range of practices and materials have been used throughout history. Furthermore, the ability to heal wounds quickly is among the most appealing of all technologies imagined by science fiction movies such as *Transcendence* (Pfister W, 2014) and *Star Trek* episodes. Such advanced technology is mostly based on the use of nanotechnology or nanomedicine.<sup>3</sup> Current research investigating ways of hastening the wound healing process continues to increase with advances in technology. The development of complex materials on a nanoscale (1–100 nm) provides a means capable of facilitating migration and proliferation through the controlled release of cytokines and growth factors such as endothelial growth factor, insulin-like growth factor, transforming growth factor and fibroblast growth factor, which form the complex signalling network that alters the growth, differentiation, and metabolism of targeted cells and prevents excessive abnormal collagen formation.<sup>4,5</sup>

Although the present study has some limitations as it was an animal study, it offers a window to the potential consequences of preventing excessive and abnormal fibrosis after urethral trauma. As stated in the editorial comments, longitudinal, larger, well-designed randomized controlled trials certainly need to be conducted, but it can be clearly stated that the present study is the spark, having secured a tipping point, because of the similarity of nano-technology methodology for the wound healing process. Many of the most significant developments begin with small imperfect steps that become strides towards improvement.

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